The Global Scenario enables us to understand that pharmaceutical research and development has become a matter of survival keeping in view the liberalization of economic policies and maintaining a competitive edge in the International Market.

The method by which a drug is delivered can have a significant effect on its efficacy. The very slow progress in the efficacy of the treatment of severe diseases has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity and efficacy of drugs were generated. These new strategies often called Drug Delivery Systems (DDS) are based on interdisciplinary approaches that combine polymer science, pharmaceutics and molecular biology.

The Sustained Drug Delivery has been the mainstay of Pharmaceutical Research during the past few decades. Barrier related problem has been addressed by multiple approaches including alternative routes of administration. Harnessing the drug molecule for safer effective and improved therapeutics is the challenge which the Pharmaceutical Scientists are meeting successfully in fastly advancing and one of the most demanding ‘Health Care Sector’.

The pace of drug discovery has increased with the introduction of new targets and new inhibitors of those targets being reported each month. These advances have brought not only new information, but also new challenges.

Over the past two decades, fungal infections have increased significantly in frequency and causes of morbidity and mortality. As advances in medical care have improved the survival of patients with severe and life-threatening illness, the more aggressive nature of such care has led to a rapid increase in the number of immune-suppressed populations. These changes have been correlated with a substantial increase in the rate of invasive fungal infections (IFIs), mainly resulting from the rapid increase in the number of at-risk patients.

Candidiasis is one of the most common, treatable oral mucosal infections seen in persons with human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS). Candidiasis can be a frequent and significant source of oral discomfort, pain, loss of taste, and aversion to food. Candida albicans carriage and a history of oral
candidiasis are other significant risk factors for oral candidiasis. The infection is caused by *candida albicans*, a dimorphic fungal organism that typically is present in the oral cavity in a non-pathogenic state in about one-half of healthy individuals.

The First Chapter, Introduction illustrates general information on Candidiasis, the causative organism and various treatments available. It also describes principles of Mucoadhesision as well as basics of factorial design. Most of mouth infections are mainly due to candidiasis and bacterial infections. Several antifungal agents can be used topically. For topical agents, successful therapy depends on adequate contact time between the agent and the oral mucosa. Topical agents have the benefit of few side effects at normal therapeutic doses because of their lack of gastrointestinal absorption.

Systemic antifungals have the advantage of once-daily dosing and simultaneous treatment of fungal infections at multiple body sites. However, these antifungals have more side effects, and selection requires consideration of important drug interactions. The dental hygienist can play an important role in the education of patients to prevent recurrence. Candidiasis is a common oral and perioral opportunistic infection that usually results from overgrowth of endogenous Candida fungal microorganisms.

For many years, Amphotericin B deoxycholate remained the mainstay of treatment for fungal infections. The major limitations of its usage are the substantial adverse effects such as fever, chills, nausea and vomiting, electrolyte abnormalities and, most importantly, nephrotoxicity. In the 1990s, the introduction of the two azoles Fluconazole and Itraconazole represented a considerable advance in antifungal therapy. However, the use of Fluconazole is hampered by its narrow spectrum, and the use of Itraconazole is limited due to absorption problems and higher variability.

In the present study, Itraconazole has been selected as a drug as it has greater degree of variability being belonged to BCS Class III. Itraconazole is an orally active, broad-spectrum, triazole antifungal agent which is registered, or in the process of the registration, in most countries of the world. Itraconazole has a broader spectrum of activity than other azole antifungals and shows interesting pharmacokinetic features in terms of its tissue distribution. These properties have resulted in shorter treatment times in vaginal candidiasis, dermatomycosis and onychomycosis, as well as effective oral treatment of several deep mycoses, including aspergillosis, candidiasis, cryptococcosis, histoplasmosis.
Drug Delivery Systems (DDS) that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the healthcare system. The last two decades in the pharmaceutical industry have witnessed an avant-garde interaction among the fields of polymer and material science, resulting in the development of novel drug delivery systems. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, etc. which modulates the release and absorption characteristics of the drug. Microspheres constitute an important part of these particulate DDS by virtue of their small size and efficient carrier characteristics. However, the success of these novel DDS is limited due to their short residence time at the site of absorption. It would, therefore, be advantageous to have means for providing an intimate contact of the DDS with the absorbing membranes. It can be achieved by coupling bioadhesion characteristics to microspheres and developing Novel Delivery Systems referred to as ‘bioadhesive microspheres’.

The Literature Surveyed reveals that there are various methods for the preparation of solid dispersions or nano/microparticles using Eudragit polymers including solvent evaporation, co-precipitation, emulsification evaporation, emulsification-diffusion and salting-out method. Each approach has its benefits and drawbacks. Solvent evaporation is a common method to prepare solid solutions/dispersions by dissolving drug and carrier in a solvent and then evaporating the solvent. The resulting solid mass is ground and sieved. The limitations of this method have been reviewed previously. Scale-up and physical/chemical instabilities are major problems. Co-precipitates are prepared by transferring a solution of drug/polymer in a water-miscible solvent into an aqueous solution containing a stabilizer. The co-precipitates are formed instantaneously by rapid solvent diffusion. The use of low polymer solution concentrations is necessary to obtain small particles and to avoid large aggregates. For the emulsification–evaporation method, a drug/polymer solution in a water-immiscible solvent (e.g., dichloromethane) is emulsified into an aqueous solution containing an emulsifier. The subsequent evaporation of the solvent from the o/w emulsion results in the formation of nano-/microparticles. The emulsification-diffusion method is similar to the emulsification–evaporation method, but it uses a partially water soluble solvent (e.g., benzyl alcohol). A large amount of water is needed to induce diffusion of the solvent from the o/w emulsion to form nano-/microparticles.
The present study deals with preparation of microspheres by Emulsification and Solvent Evaporation Techniques which yielded microspheres with desired parameters and which are further optimized using appropriate Factorial Design Methodology.

It has been investigated that buccal mucosa can also be a potential site for controlled delivery of macromolecular therapeutic agents, such as peptides, proteins and polysaccharides because of its accessibility and low enzymatic activity compared to the gastro-intestinal tract.

Moreover, buccal drug delivery offers a safer method of drug utilization, since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally via this route. Therefore, adhesive mucosal dosage forms were suggested for oral delivery which included adhesive tablets, adhesive gels and adhesive patches.

The proposed work encapsulates experimental design involving the arrangements of experiments in the design space such that the reliable and consistent information is achievable with minimum number of experiments. No experimental design exists on its own, but is influenced by the previous phase of experimentation and the projected future steps, i.e., the choice of the design depends on the proposed model, shape of the domain and the objectives of the study. Experimental designs are based on the principles of randomization, replication and error control. Experimental run or trial is a practical manipulation carried out under defined conditions, resulting in the data for each of the response to be measured.

The Second Chapter deals with the details of drug Itraconazole and its innovator taken for the present research work and preformulation studies. Itraconazole is a white or almost white powder, practically insoluble in water, very slightly soluble in alcohol, freely soluble in dichloromethane, sparingly soluble in tetrahydrofuran. The brand name for Itraconazole is Sporanox® manufactured by Jannsen Pharmaceuticals. The drug is having molecular weight of 705.64 and has pKa value of 3.70. The melting point of drug is between 166°C to 170°C.

Itraconazole is absorbed from gastrointestinal tract when administered by mouth either as capsules containing Itraconazole onto sugar spheres or as an oral liquid formulations with hydroxyl propyl-β-cyclodextrin. Itraconazole is highly protein bound; only 0.2% circulates as free drug. Itraconazole is widely distributed but only small amounts diffuse into
CSF. Absorption from the capsule formulation is enhanced by acidic gastric environment and is greatest when doses are taken with food. Itraconazole belongs to the category of highly variable drugs.

Not much work has been done in this direction to design a dosage form so as to release the drug in a controlled manner reducing intra-patient variability. It has been therefore decided to focus the limelight on releasing the drug in a controlled manner via various approaches to reduce the variability of the drug as reported in few trials.

The studies focus on those physiological properties of the new compound that could affect drug performance and development of an efficacious dosage form. The tests carried out include infrared spectroscopy and melting point determination. Solubility behavior of the drug was also studied and the drug as per literature was found to be poorly soluble. The partition coefficient which was the measure of degree of lipophilicity was determined using n-octanol and water and was found to be 5.31. Drug excipients interaction studies were also studied. DSC study was carried out to determine compatibility between drugs and polymers involved in the study. The chapter also details about the $3^2$ factorial design, various combinations studied and DOE widely used in pharmaceutical field to study the effect of formulation variables and their interaction on response variables. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses as per equation:

$$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_{12}X_1X_2 + \beta_{11}X_{12} + \beta_{22}X_{22}$$

Where, Y is the dependent variable, $\beta_0$ is the arithmetic mean response of nine runs

Factorial combinations of Mucoadhesive microspheres, Eudragit based microspheres and Mucoadhesive patches were studied with level of low, medium and high. The polymer used for design of Mucoadhesive microspheres are HPMC5CP, HPMCK4M and HPMC10CP grades. For Eudragit based microspheres the polymers used are RS30D, EPO and E100 grades. For Mucoadhesive patches polymers used are PVPHPMC50CP, PVPPNaCMC and PVPHPMCK4M.

Various process variables which could influence the preparation and properties of microspheres were identified and optimized. The optimization was carried out by varying one parameter while keeping other constant. In-vitro characterization was done by studying shape and surface morphology, particle size distribution, drug loading capacity and encapsulation efficiency, degree of swelling, in-vitro drug release, drug release kinetics and in-vitro
Mucoadhesion studies. The patches were evaluated for mass uniformity and patch thickness, surface pH, viscosity, folding endurance test, swelling, residence time, bioadhesion force and in-vitro release study.

The present study provides detail on the physic chemical properties of the drug. The identification tests reveal that the drug complies with the official standard. Melting point determination using melting point apparatus was found to be 168°C. The infrared spectrum of drug was found to be identical to that reported literature in confirming identity and purity of drug. The solubility determined the type of method to be followed or solvent to be employed for designing and developing formulation. Selection of solvent exhibits an influential role in the performance of delivery system. The absorption maxima of drug were reduced while scanning a 0.001% w/v drug solution within a range of 200-400 nm using double beam spectrophotometer. The value of $\lambda_{\text{max}}$ was found to be 264 nm in Simulated Gastric Fluid without enzyme.

The media selected for the research work is Simulated Gastric Fluid without Enzyme (pH 1.5). The media has been selected on the basis of literature available from Office of Generic Drugs (OGD). Although attempts has been also made to study dissolution behavior in pH 6.8 phosphate buffer containing a suitable solubilizer.

Various calibration curves of drug in solution of different pH values were constructed. It was observed that drug in concentration of 2-20µg/ml obeys Beer’s Lambert law. The linearly regressed calibration curves were plotted and calculated correlation coefficient which was found to be in the range of 0.9996 to 0.9999 showing good linearity between concentration and absorbance within the concentration range 2-20µg/ml. The standard error value indicates good reproducibility of the data as on running experiments in triplicates. The calibration curve was prepared in Simulated Gastric Fluid pH 1.5 and 6.8 pH phosphate buffer (containing 1% SLS). The absorbance was measured at concentration range of 1 - 10µg/ml. The calculation of in-vitro drug release and drug content were based on respective calibration curves. The correlation coefficient value for Itraconazole was found to be 0.998 and 0.999 in Simulated Gastric Fluid pH 1.5 and 6.8 pH phosphate buffer respectively.

An attempt was made to study interaction of drug with the polymers. The drug is distributed in the matrix of polymer and any interaction of the drug with the polymer can lead
to anomaly in the performance of the designed delivery system. In the present investigation, the interaction of the drug with the polymer was determined by incubating the drug with polymers which revealed that an insignificant amount (p>0.05) of drug was bound to polymer. The amount of drug remained after 24, 48 and 72 hrs was found to be 99.6, 99.5 and 99.1 respectively. Similarly interaction of drug with other excipients was performed.

In the present investigation, Differential Scanning Calorimetry studies were also carried out to determine the thermal behavior of the pure drug, and along with different excipients to check the compatibility of drug with rest of excipients. In the thermogram of Itraconazole a sharp endothermic peak at 167.65°C is obtained which is a characteristic peak of Itraconazole. DSC of Itraconazole along with polymer (Chitosan) revealed that there has been no considerable change in peak value which was found to be 167.47°C as compared to 167.65°C for pure drug. This indicates compatibility of drug with polymer. DSC studies of another polymer (HPMC) used for preparation of buccal films indicates further no change in peak of drug which was found to be 167.75°C indicating compatibility of drug with polymer.

The DSC studies also revealed that the polymers (Hydroxy propyl methyl cellulose, Chitosan are compatible) having no interaction with the drug candidate (Itraconazole). Interactions in the sample are indicated from DSC curves by change in thermal events such as elimination of an endothermic or exothermic peak or appearance of a new peak. In the first phase of the study, compatibility of drug and polymer physical mixture was tested using the ratio 1:1. Thermal curve of ITCZ displayed single sharp peak (T peak = 167.69°C; T onset = 164.50°C). The interactions between ITCZ and a distinct polymer mixture [1:1 (% w/w)] were then investigated by DSC. Regarding the drug: polymer mixtures (1:1) studied, the corresponding thermograms were found not to be a simple superposition of those obtained for each component separately. Reduction peak and enthalpy values may be attributed to the mixing process that lowers the purity of each component in the mixture. Overall, the DSC study for polymers alone and their physical mixtures with drug at ratio 1:1 % w/w revealed that, the polymers (Hydroxy Propyl Methyl Cellulose, Chitosan) are compatible, having no interaction with the drug candidate (Itraconazole). Furthermore it is suggested that it can be successfully utilized in the formulations of Itraconazole with above mentioned polymers.

Furthermore, Fourier Transform Infrared was also carried out to draw information on the molecular state of Itraconazole and mixture of Itraconazole and Chitosan and HPMC.
In FTIR spectrum chitosan exhibited a broad peak at 3431 cm\(^{-1}\) which is assigned to the N-H and hydrogen bonded O-H stretch vibrational frequencies, while a sharp peak at 3610 cm\(^{-1}\) is that of free O-H bond stretch of glucopyranose units. Further, in the C-H stretch region of FTIR spectrum, the higher intensity peak at 2923 cm\(^{-1}\) is assigned to the asymmetric and the lower intensity peak at 2857 cm\(^{-1}\) is assigned to the symmetric modes of CH\(_2\). The peaks at 1550 and 1599 cm\(^{-1}\) were assigned to strong N-H bending vibrations of secondary amide, which usually occur in the range of 1640 to 1550 cm\(^{-1}\) as strong band. The characteristic IR peak of ITCZ alone over the frequency range 500-4000 cm\(^{-1}\) occurred at 3439, 3126 and 3069 cm\(^{-1}\) due to the absorption of NH\(_2\) groups, 2964 cm\(^{-1}\) resulted from CH\(_2\) stretching frequency band and a sharp peak occurred at 1698 cm\(^{-1}\) due to C=O stretching vibration. The peaks observed at 1609 cm\(^{-1}\) and 1429 cm\(^{-1}\) may be assigned to the C=N and C-N bonds, respectively. The characteristic peaks occurred at 1510 and 1451 cm\(^{-1}\) owed to C-H deformation. The IR region from 600 – 1400 cm\(^{-1}\) which is called the fingerprint, usually contains a large number of unassigned vibrations characteristic of the molecule.

The results revealed the IR spectra of the physical mixtures of ITCZ with HPMC and Chitosan did not show any significant differences in the characteristic bands of the respective spectra of the pure components and the functional groups still showing their characteristic bands indicating that there is no complex formation. FTIR spectra of HPMC gave the characteristic peaks at about 1643, 1109 and 1033 cm\(^{-1}\) vibration region.

The formulations were optimized using response surface methodology and the results were studied after reviewing ANOVA, Diagnostic case statistics and Contour plots.

The Model F-value of 41.37 implies the model is significant. There is only a 0.57% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case B, AB, A\(^2\), B\(^2\) are significant model terms. The results of ANOVA for response surface quadratic model of Microencapsulation Efficiency of ITCZ-HPMC5CP microspheres exhibits the SS and F-value for full quadratic model was investigated as 325.78 and 41.37 which is a good indicator of freedom of analysis. The quadratic model was found to be significant with p<0.01. The results of diagnostic case statistics shows that the predicted (theoretical) and actual (practical) values are in limits, except standard order number 2, 4, 8 and 9 are statistically exceeding the limits.
The results are visualized in 3-D surface plot and indicated that the % Microencapsulation Efficiency is dependent on both factors.

The Model F-value of 7.47 implies there is a 6.43% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In this case B$^2$ are significant model terms. The results of ANOVA for response surface quadratic model of Microencapsulation Efficiency of ITCZ-HPMCK4M microspheres shows the sum of squares (SS) and F-value for full quadratic model was investigated at 388.79 and 77.76 which was investigated at p<0.5. The sum of squares of B$^2$ (stirring speed) estimated at 302.33 and F-value found to be 29.03 with good freedom of analysis, suggesting that stirring speed significant term in this quadratic model at p<0.05. The interaction term AB and polynomial term A$^2$ and B$^2$ were also estimated and found to be insignificant at level p<0.1. From these results, it can be concluded that the predicted and actual values are in limits with some exceptions. The 3-D plot indicated that the Microencapsulation Efficiency depends predominantly on stirring speed.

The Model F-value of 5.51 implies there is a 9.53% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In this case B is significant model terms. The sum of squares (SS) and F-value for full quadratic model was investigated at 617.12 and 26.05 which was investigated at p<0.05. The interaction term AB and polynomial term A$^2$ and B$^2$ were also estimated and found to be insignificant. The observation of diagnostic case statistics concludes that the predicted and actual values are in limits with some exceptions. The 3-D plot indicated that the Microencapsulation Efficiency depends predominantly on stirring speed.

The Correlation Coefficient of Microencapsulation Efficiency of ITCZ-HPMC5CP, ITCZ-HPMCK4M and ITCZ-HPMC10CP were 0.9857, 0.9256 and 0.9018 respectively with maximum for ITCZ-HPMC5CP and were good indicator of fit and factors such as Stirring speed and Polymer concentration greatly control the process.

The results of ANOVA for response surface quadratic model of Microencapsulation Efficiency of ITCZ-RS30D microspheres found to have the SS and F-value for full quadratic model as 217 and 43.4 which is a good indicator of freedom of analysis. The quadratic model was found to be significant with p<0.5. The results are visualized in 3-D surface plot which indicated that, the % Microencapsulation Efficiency is dependent on both factors.
The Model F-value of 8.70 implies there is a 5.24% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In this case A, B^2 are significant model terms. The results of ANOVA for response surface quadratic model of Microencapsulation Efficiency of ITCZ-EPO microspheres have SS and F-value for full quadratic model at 404.83 and 80.97 which was investigated at p<0.5. The polymer concentration estimated at 113.97 and F-value found to be 12.25 with good freedom of analysis, suggesting that stirring speed significant term in this quadratic model at p<0.05. The interaction term B^2 were also estimated and found to be insignificant at level p<0.1. The observation of diagnostic case statistics concludes that the predicted and actual values are in limits with some exceptions. The 3-D plot indicated that the Microencapsulation Efficiency depends predominantly on stirring speed and polymer concentration.

The "Model F-value" of 1.66 implies the model is not significant relative to the noise. There is a 35.80 % chance that a "Model F-value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In this case there are no significant model terms. The results of ANOVA for response surface quadratic model of Microencapsulation Efficiency of ITCZ-E100 microspheres have SS and F-value for full quadratic model was investigated at 168.42 and 33.68 which was investigated at p<0.5. No significant model terms are detected.

The Correlation Coefficient of Microencapsulation Efficiency of ITCZ-RS30D, ITCZ-EPO and ITCZ-E100 were 0.8687, 0.9355 and 0.7351 respectively with maximum for ITCZ-EPO and were good indicator of fit and factors such as Stirring speed and Polymer concentration greatly control the process.

Swelling Efficiency was determined for Buccal patches prepared using Polyvinylpyloridone and HPMC50CP, NaCMC and HPMCK4M which was found in range of 35.54 to 44.92, 27.16 to 34.10 and 7.87 to 12.24 respectively. The "Model F-value" of 0.93 implies the model is not significant relative to the noise. There is a 56.02 % chance that a "Model F-value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In this case there are no significant model terms. The results of ANOVA for response surface quadratic model of Degree of Swelling of ITCZ-NaCMC patches exhibits the SS and F-value for full quadratic model as 56.62 and 11.32.
The results are visualized in 3-D surface plot which indicated that the Degree of Swelling is dependent on both factors (A and B). Assessment of swelling behavior was done by measuring radial swelling. The water soluble polymer dissolves rapidly introducing porosity. The void volume is thus expected to be occupied by the external solvent diffusing into the film and thereby accelerating the dissolution of gel. Incorporation of drug in the film along with polymer exhibits varied swelling behavior.

The "Model F-value" of 0.70 implies the model is not significant relative to the noise. There is a 66.11 % chance that a "Model F-value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In this case there are no significant model terms. The results of ANOVA for response surface quadratic model of Degree of Swelling of ITCZ-HPMC50CP patches exhibits the SS and F-value for full quadratic model as 18.28 and 3.66. No significant model terms were estimated. The results are visualized in 3-D surface plot which indicated that the Degree of Swelling is dependent on both factors.

The "Model F-value" of 2.12 implies the model is not significant relative to the noise. There is a 28.42 % chance that a "Model F-value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In this case there are no significant model terms. The results of ANOVA for response surface quadratic model of Degree of Swelling of ITCZ-PVPHPMC50CP patches have the SS and F-value for full quadratic model was investigated as 15.81 and 3.16. The results are visualized in 3-D surface plot which indicated that the Degree of Swelling is dependent on both factors.

The Correlation Coefficient of Degree of Swelling of ITCZ-PVPHPMC50CP, ITCZ-PVPNaCMC and ITCZ-PVPHPMC50M were 0.6086, 0.5387 and 0.7798 respectively with maximum for ITCZ-PVPHPMC50M and were good indicator of fit and factors such as Stirring speed and Polymer concentration greatly control the process.

Mucoadhesion time was determined for formulation codes ITCZ-PVPHPMC50CP, ITCZ-PVPNaCMC and ITCZ-PVPHPMC50M which was found to be in range of 3.8 to 5.0, 5.3 to 7.0 and 7.1 to 8.1h respectively. The "Model F-value" of 1.25 implies the model is not significant relative to the noise. There is a 45.45 % chance that a "Model F-value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In this case there are no significant model terms. The results of ANOVA for
response surface quadratic model of Mucoadhesion time of ITCZ-PVPHPMC50CP patches are found to be having the SS and F-value for full quadratic model as 1.19 and 0.24. No significant model terms were estimated. The results are visualized in 3-D surface plot which indicated that, the *Ex-vivo* Mucoadhesion time is dependent on both factors.

The "Model F-value" of 1.65 implies the model is not significant relative to the noise. There is a 36.16% chance that a "Model F-value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In this case there are no significant model terms. The results of ANOVA for response surface quadratic model of Mucoadhesion time of ITCZ-PVPNaCMC patches are having the SS and F-value for full quadratic model as 1.59 and 0.32. The results are visualized in 3-D surface which indicated that, the *Ex-vivo* Mucoadhesion time is dependent on both factors.

The Model F-value of 6.71 implies there is a 7.40% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In this case $B^2$ are significant model terms. The results of ANOVA for response surface quadratic model of Mucoadhesion time of ITCZ-PVPHPMCK4M patches have the SS and F-value for full quadratic model was investigated as 1.19 and 0.24 which is a good indicator of freedom of analysis. The value for $B^2$ was estimated at 0.72 with F value of 20.25 indicating $p<0.05$. The results are visualized in 3-D surface plot which indicated that *Ex-vivo* Mucoadhesion time is dependent primarily on concentration of polymer HPMCK4M.

The Correlation coefficient of *Ex-vivo* Mucoadhesion time of ITCZ-PVPHPMC50CP, ITCZ-PVPNaCMC and ITCZ-PVPHPMCK4M were 0.6761, 0.7329 and 0.9179 respectively and was maximum in case of ITCZ-PVPHPMCK4M and were good indicator of fit and factors such as both polymer concentrations greatly control the process.

The "Model F-value" of 1.93 implies the model is not significant relative to the noise. There is a 31.21% chance that a "Model F-value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In this case there are no significant model terms. The results of ANOVA for response surface quadratic model of Particle size of ITCZ-HPMC5CP microspheres exhibits the SS and F-value for full quadratic model was investigated as 9784.29 and 1956.86. The results are visualized in 3-D surface plot which indicated that Particle size time is dependent primarily on concentration of polymer concentration and stirring speed.
The Model F-value of 5.62 implies there is a 9.30% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In this case B are significant model terms. The results of ANOVA for response surface quadratic model of Particle size of ITCZ-HPMCK4M microspheres have the SS and F-value for full quadratic model was investigated as 44653.88 and 8930.78 which is a good indicator of freedom of analysis. The value for stirring speed was estimated at 40101.65 with F value of 25.25 indicating p<0.05. The results are visualized in 3-D surface plot which indicated that particle size is dependent primarily on stirring speed.

The "Model F-value" of 4.35 implies the model is not significant relative to the noise. There is a 12.81 % chance that a "Model F-value" this large could occur due to noise. Values of "Prob > F" less than 0.050 indicate model terms are significant. In this case B are significant model terms. The results of ANOVA for response surface quadratic model of Particle size of ITCZ-HPMC10CP microspheres have the SS and F-value for full quadratic model was investigated as 37227.86 and 7445.57 which is a good indicator of freedom of analysis. The value for stirring speed was estimated at 33874.61 with F value of 19.78 indicating p<0.05. The results are visualized in 3-D surface plot which indicated that Particle size is dependent primarily on stirring speed.

The Correlation Coefficient of Particle size analysis of ITCZ-HPMC5CP, ITCZ-HPMCK4M and ITCZ-HPMC10CP were 0.7628, 0.9036 and 0.8787 respectively with maximum for ITCZ-HPMCK4M and were good indicator of fit and factors such as Stirring speed and Polymer concentration greatly control the process.

The Model F-value of 9.46 implies the model is significant. There is only a 4.69% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In this case B are significant model terms. The results of ANOVA for response surface quadratic model of Particle size of ITCZ-RS30D microspheres shows the SS and F-value for full quadratic model was investigated at 42443.26 and 8488.65 which was investigated at p<0.5. The model term stirring speed estimated at 40692.43 and F-value found to be 45.33 with good freedom of analysis, suggesting that stirring speed significant term in this quadratic model at p<0.01. The 3-D plot indicated that the Particle size depends predominantly on stirring speed.
The Model F-value of 13.63 implies the model is significant. There is only 2.83% chance that a "Model F-Value" this large could occur due to noise. Values of Prob > F less than 0.05 indicate model terms are significant. In this case B are significant model terms. The results of ANOVA for response surface quadratic model of particle size of ITCZ-EPO microspheres have the SS and F-value for full quadratic model was investigated at 36384.86 and 7276.97 which was investigated at p<0.5. The model term stirring speed estimated at 32737.71 and F-value found to be 61.31 with good freedom of analysis, suggesting that stirring speed significant term in this quadratic model at p<0.01. The 3-D plot indicated that the Particle size depends predominantly on stirring speed.

The results of ANOVA for response surface quadratic model of particle size of ITCZ-E100 microspheres exhibits the SS and F-value for full quadratic model was investigated at 6173.92 and 1234.78 which was investigated at p<0.5. The model term (B^2) was stirring speed estimated at 3695.71 and F-value found to be 25.21 with good freedom of analysis, suggesting that stirring speed significant term in this quadratic model at p<0.05. The 3-D plot indicated that the Particle size depends predominantly on stirring speed.

The Correlation Coefficient of Particle size analysis of ITCZ-PVPHPMC50CP, ITCZ-PVPNaCMC and ITCZ-PVPHPMCK4M were 0.9403, 0.9578 and 0.9335 respectively and were good indicator of fit and factors such as Stirring speed and Polymer concentration greatly control the process.

In-vitro drug release study is performed to calculate in-vivo behaviour of drug. A number of pharmacoeipal methods have been proposed for dosage form based drug dissolution studies. As per ICH guidelines, pH 1.2, 4.5 and 6.8 were used to predict in-vivo drug dissolution behaviour of modified release drug products. Mucoadhesive microspheres and Eudragit based formulations were evaluated in Simulated Gastric Fluid pH 1.5. The drug used in present research work exhibits pH dependent solubility.

The "Model F-value" of 4.55 implies the model is not significant relative to the noise. There is a 12.11% chance that a "Model F-value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In case of ITCZ-HPMC5CP microspheres B are significant model terms. The Model F-value of 16.27 implies the model is significant. There is only a 2.20% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are
significant. In case of ITCZHPMCK4M microspheres A are significant model terms. The Model F-value of 6.99 implies there is a 7.02% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In case of ITCZ-HPMC10CP microspheres B are significant model terms.

The results of ANOVA for response surface quadratic model of Drug Release of ITCZ-HPMC5CP, ITCZ-HPMCK4M and ITCZ-HPMC10CP microspheres respectively. The sum of squares (SS) and F-value for full quadratic model was investigated at 18.27 and 3.65, 21.18 and 4.24 and 5.61 and 1.12 respectively which was investigated at p<0.5 for ITCZ-HPMCK4M microspheres. For ITCZ-HPMC5CP microspheres, the model term B was stirring speed estimated at 12.62 and F-value found to be 15.72 with good freedom of analysis, suggesting that stirring speed significant term in this quadratic model at p<0.05. For ITCZ-HPMCK4M microspheres, the model term A was polymer concentration estimated at 17.34 and F-value found to be 66.6 with good freedom of analysis, suggesting that stirring speed significant term in this quadratic model at p<0.01. For ITCZ-HPMC10CP microspheres, the model term B was stirring speed estimated at 3.08 and F-value found to be 19.18 with good freedom of analysis, suggesting that stirring speed significant term in this quadratic model at p<0.01. The 3-D indicated that the Drug Release depends predominantly on stirring speed and polymer concentration.

The Model F-value of 22.48 implies the model is significant. There is only a 1.39% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In case of ITCZ-RS30D microspheres A, B, B^2 are significant model terms. The Model F-value of 69.90 implies the model is significant. There is only a 0.26% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In case of ITCZ-EPO microspheres A, B, B^2 are significant model terms. The Model F-value of 46.67 implies the model is significant. There is only a 0.48% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In case pf ITCZ-E100 micropsheres A, B are significant model terms.

The results of ANOVA for response surface quadratic model of Drug Release of ITCZ-RS30D, ITCZ-EPO and ITCZ-E100 microspheres respectively. The sum of squares (SS) and F-value for full quadratic model was investigated at 8.81 and 1.76, 12.65 and 2.53
and 15.82 and 3.16 respectively which was investigated at p<0.5 for all formulations. The model term A and B found to having F-value with good freedom of analysis, suggesting that stirring speed significant term in this quadratic model at p<0.05. The 3-D plot indicated that the drug release depends predominantly on stirring speed and polymer concentration.

The "Model F-value" of 5.23 implies the model is not significant relative to the noise. There is a 10.19 % chance that a "Model F-value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In case of ITCZ-PVPHPMC50CP patches, B, B^2 are significant model terms. The Model F-value of 11.17 implies the model is significant. There is only a 3.73% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In case of ITCZ-PVPNaCMC patches, B, B^2 are significant model terms. The Model F-value of 7.93 implies there is a 5.93% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. In case of ITCZ-PVPHPMCK4M patches B are significant model terms. The results of ANOVA for response surface quadratic model of particle size of ITCZ-PVPHPMC50CP, ITCZ-PVPNaCMC and ITCZ-PVPHPMCK4M patches respectively. The sum of squares (SS) and F-value for full quadratic model was investigated at 8.56 and 5.23, 7.03 and 11.17 and 9.04 and 7.93 respectively which was investigated at p<0.5 for all formulations. The 3-D plot indicated that the Drug Release depends predominantly on polymer concentration.

The Correlation Coefficient of Drug Release of ITCZ-PVPHPMC50CP, ITCZ-PVPNaCMC and ITCZ-PVPHPMCK4M were 0.8971, 0.949 and 0.9297 respectively with maximum for ITCZ-PVPNaCMC and were good indicator of fit and factors such as polymer concentration greatly control the process.

In-vitro dissolution studies are a measure of quality control of product consistency and results can be correlated with in-vivo performance of the drug. Dissolution apparatus varies with the formulation type and no single apparatus can be used for all formulations. Modifications are therefore necessary to build a good in-vitro in-vivo correlation which is considered as a preliminary step in successful design of dosage forms. Literature survey revealed that abundant reports of predominant use of only one or two pH stages (mostly pH 1.2, 6.8 and 7.4) for the evaluation of sustained release formulations. The Drug release for
microspheres was evaluated in pH 1.5 Simulated Gastric Fluid without enzyme. The drug in present study shows solubility in acidic pH. Hydroxy propyl methyl cellulose and Eudragit grade polymers are widely used as a matrix in controlled release systems due to their hydrophilic nature and fast hydration which act as excellent matrix forming agent in different formulation in combinations. Results indicated that microspheres formulated using low drug to polymer ratio and high stirring speed yielded smaller microspheres which quickly release drug due to increase in surface area. Initial drug release may be from unencapsulated drug. The second phase of release process is slow and can be attributed to diffusion process of encapsulated drug from microspheres. The Eudragit polymer based grades namely EPO and E100 dissolves at acidic pH and was unique in its kind in form of microspheres exhibiting controlled release over a period of time. Eudragit RS30D polymer exhibit pH independent behavior although the drug release was initially slow and erratic as compared to HPMC polymer based microspheres which were also evident from scanning electron microscopic observation showing non uniformity on surface.

The Buccal films were also developed having weight in range of 240±0.4 to 298±0.6 mg. The surface pH of the film was found to be in range of 6.0 to 7.0 for all formulations. The film pH is closed to the physiological pH of buccal mucosa. Hence, these films don’t cause irritation to mucosa. Optical microscopy reveals that the buccal films do have some irregularities at the surface which may be attributed to polymeric behavior. The surface adsorbed drug may be the reason for quick initial release of drug. On keeping the films in dissolution medium the drug starts dissolving and polymer starts eroding slowly.

Film Mucoadhesion varies from 3.8 to 5 h, 5.3 to 7 h and 7.1 to 8.1 h for formulation codes ITCZ-PVPHPMC50CP, ITCZ-PVPNaCMC and ITCZ-PVPHPMCK4M respectively. The greater Mucoadhesion for ITCZ-PVPHPMCK4M may be attributed to greater viscosity of K4M grade as compared to other polymers. The Mucoadhesion varied for various formulations due to polymeric behavior which favors hydration and outward diffusion of drug from matrix.

The characteristics of polymer influence the nature of film in terms of uniformity and permeability. They employed HPMC and NaCMC in their buccal formulations and observed that Mucoadhesion time in case of HPMC was higher than NaCMC. Chitosan is a promising bioadhesive material at neutral or slightly alkaline pH, which is found to be
advantageous for adsorption on the mucosal surface. It was suggested that, at this pH, chitosan exhibits numerous amine and hydroxyl groups that may increase the interaction of polymer with the negative mucin. The rheological interaction between chitosan and mucin, and/or hydrophillic additives and mucin produces strong force of attraction between polymer and mucus membrane and in turn influences Mucoadhesive property of the films.

Drug Release behavior depends primarily on drug:polymer concentration (1:1, 1:2 and 1:3). At low drug:polymer ratio (1:1) formulations ITCZ-HPMC5CP1, ITCZ-HPMCK4M1, ITCZ-HPMC10CP1, ITCZ-RS30D1, ITCZ-EPO1, ITCZ-E1001, ITCZ-PVPHPMC50CP1, ITCZ-PVPNaCMC1 and ITCZ-PVPHPMCK4M1 shows drug release of 60.91, 68.77, 84.57, 59.18, 71.03, 80.01, 76.65, 66.86 and 45.02 respectively. For formulation codes ITCZ-HPMC5CP4, ITCZ-HPMCK4M4, ITCZ-HPMC10CP4, ITCZ-RS30D4, ITCZ-EPO4, ITCZ-E1004, ITCZ-PVPHPMC50CP4, ITCZ-PVPNaCMC4 and ITCZ-PVPHPMCK4M4 drug release was found to be 68.53, 73.30, 90.39, 70.29, 73.75, 77.53, 66.60, 74.47 and 61.76 respectively. For formulation codes ITCZ-HPMC5CP7, ITCZ-HPMCK4M7, ITCZ-HPMC10CP7, ITCZ-RS30D7, ITCZ-EPO7, ITCZ-E1007, ITCZ-PVPHPMC50CP7, ITCZ-PVPNaCMC7 and ITCZ-PVPHPMCK4M7 was 77.03, 72.86, 86.38, 72.04, 73.52, 84.53, 78.83, 68.39 and 69.39 respectively. For drug polymer ratio (1:2) formulation codes ITCZ-HPMC5CP2, ITCZ-HPMCK4M2, ITCZ-HPMC10CP2, ITCZ-RS30D2, ITCZ-EPO2, ITCZ-E1002, ITCZ-PVPHPMC50CP2, ITCZ-PVPNaCMC2 and ITCZ-PVPHPMCK4M2 drug release was found to be 58.39, 65.80, 79.24, 54.53, 59.43, 72.88, 66.60, 60.48 and 54.43 respectively. For formulation codes ITCZ-HPMC5CP6, ITCZ-HPMCK4M6, ITCZ-HPMC10CP6, ITCZ-RS30D6, ITCZ-EPO6, ITCZ-E1006, ITCZ-PVPHPMC50CP6, ITCZ-PVPNaCMC6 and ITCZ-PVPHPMCK4M6 68.57, 75.52, 82.58, 67.38, 66.62, 69.45, 69.09, 68.84 and 60.18 respectively. For formulation codes ITCZ-HPMC5CP9, ITCZ-HPMCK4M9, ITCZ-HPMC10CP9, ITCZ-RS30D9, ITCZ-EPO9, ITCZ-E1009, ITCZ-PVPHPMC50CP9, ITCZ-PVPNaCMC9 and ITCZ-PVPHPMCK4M9 76.25, 64.53, 83.93, 68.51, 58.50, 81.00, 82.20, 69.39 and 66.86 respectively. For drug polymer concentration (1:3) for formulation codes ITCZ-HPMC5CP4, ITCZ-HPMCK4M4, ITCZ-HPMC10CP4, ITCZ-RS30D4, ITCZ-EPO4, ITCZ-E1004, ITCZ-PVPHPMC50CP4, ITCZ-PVPNaCMC4 and ITCZ-PVPHPMCK4M4 drug release was found to be 52.82, 51.04, 71.65, 49.67, 51.53, 56.88, 73.34, 69.04 and 48.29 respectively. For formulation codes ITCZ-HPMC5CP7, ITCZ-HPMCK4M7, ITCZ-HPMC10CP4, ITCZ-RS30D4, ITCZ-EPO4, ITCZ-
E1004, ITCZ-PVPHPMC50CP4, ITCZ-PVPNaCMC4 and ITCZ-PVPHPMCK4M4 drug release was 55.23, 68.61, 79.13, 59.37, 58.63, 63.25, 62.22, 77.96 and 64.43 respectively. For formulation codes ITCZ-HPMC5CP9, ITCZ-HPMCK4M9, ITCZ-HPMC10CP9, ITCZ-RS30D9, ITCZ-EPO9, ITCZ-E1009, ITCZ-PVPHPMC50CP9, ITCZ-PVPNaCMC9 and ITCZ-PVPHPMCK4M9 drug release was 74.84, 59.29, 75.90, 62.57, 56.69, 74.11, 73.33, 72.45 and 54.53 respectively for 12 hrs.

On the basis of R value, the best fit model for ITCZ-PVPHPMC5CP were pepas model (ITCZ-HPMC5CP1, 2, 3, 4, 5, 6, 8 and 9) and Hixson crowell model (ITCZ-HPMC5CP7). The best fit model in case of ITCZ-HPMCK4M were pepas model (ITCZ-HPMCK4M1, 2, 3, 4, 6 and 8) Hixson crowell (ITCZ-HPMCK4M5 and 7) and first order model (ITCZ-HPMCK4M9). In case of ITCZ-HPMC10CP pepas model (ITCZ-HPMC10CP1, 2, 3, 4, 5, 6, 7, 8 and 9). The best fit model in case of ITCZ-RS30D were pepas model (ITCZ-RS30D1, 2, 3, 5, 7, 8 and 9) Hixson crowell (ITCZ-RS30D4) and first order model (ITCZ-RS30D6). For ITCZ-EPO the best fit model were pepas (ITCZ-EPO1, 2, 3, 4, 5, 6, 7, 8 and 9). For ITCZ-PVPHPMC50CP the best fit model is pepas (ITCZ-PVPHPMC50CP1, 2, 3, 5, 6,7,8,9) and Hixson crowell model (ITCZ-PVPHPMC50CP4). For ITCZ-PVPNaCMC the best fit models were pepas (ITCZ-PVPNaCM1, 2 and 8) and Hixson crowell model (ITCZ-PVPNaCMC3, 4, 5, 6, 7 and 9). For ITCZ-PVPHPMCK4M, pepas model (ITCZ-PVPHPMCK4M1, 3, 4, 6, 7 and 8) and first order model (ITCZ-PVPHPMCK4M2, 5 and 9).

Cumulative Percentage Drug Release studies was also carried out for HPMC Mucoadhesive microspheres, Eudragit based Mucoadhesive microspheres and for Buccal patches. Drug release studies were carried out in respect to time taken to release 50% of drug. The coefficient of regression analysis was also estimated and was found to be 0.8835, 0.9644 and 0.9209 for formulation codes ITCZ-HPMC5CP, ITCZ-HPMCK4M and ITCZ-HPMC10CP respectively. The coefficient of regression analysis was 0.9740, 0.9915 and 0.9873 for ITCZ-RS30D, ITCZ-EPO and ITCZ-E100 formulations. The coefficient of regression analysis was 0.8971, 0.9490 and 0.9297 for formulation codes ITCZ-PVPHPMC50CP, ITCZ-PVPNaCMC and ITCZ-PVPHPMCK4M respectively. On the dissolution profiles obtained drug release kinetics study were carried out in terms of Zero order, First order, Matrix, Peppas and Hixon-crowell equations.
The results of Numerical Optimization revealed that the solutions obtained are based on overall ANOVA, Diagnostic case statistics and desirability of the model. The desirability is an objective function that ranges from zero (outside the limit values) to one (at the goal). The Numerical optimization finds a point that maximizes the desirability function. A desirability value of one doesn’t always reflect the good optimization conditions because it is completely dependent on how closely the lower and upper limit that are set relative to the actual optimum conditions.

The goal of Optimization is to find good set of conditions that will meet all goals. The formulations were selected on the basis of goals set for all responses obtained, criteria of attaining maximum microencapsulation efficiency, lowest possible particle size, best degree of swelling, better Mucoadhesion capacity and maximum time to reach half quantity of drug for sustain drug release.

The lower and upper limits of responses for microencapsulation efficiency of ITCZ-HPMC5CP, ITCZ-HPMCK4M and ITCZ-HPMC10CP were 60.42 to 79.32, 64.09 to 83.64 and 51.34 to 78.34 respectively. Particle size analysis results for above formulations were in range of 125.65 to 228.15, 121.69 to 354.18 and 145.32 to 302.49 respectively. \( t_{50} \) range for above formulations were 6.9 to 11.4, 6.7 to 11.5 and 4.9 to 7.6 respectively. For formulation codes ITCZ-RS30D, ITCZ-EPO and ITCZ-E100 microencapsulation efficiency was found to be 53.57 to 68.33, 54.97 to 76.76 and 48.22 to 65.23 respectively.

For formulations developed the range for particle size was from 133.27 to 330.87, 112.18 to 307.18 and 86.39 to 164.29 respectively. \( t_{50} \) range for above formulations were 8.7 to 12, 7.7 to 11.7 and 4.7 to 9.2 respectively. Swelling efficiency for ITCZ-PVPHPMC50CP, ITCZ-PVPNaCMC and ITCZ-PVPHPMC5CMK4M was in range of 35.54 to 44.92, 27.16 to 34.10 and 7.87 to 13.04 respectively. Ex-vivo Mucoadhesion time for above formulations was 3.8 to 5.1, 5.3 to 7.0 and 6.9 to 8.1 respectively. \( t_{50} \) range for above formulations was in range of 6 to 8.7, 7.2 to 10.1 and 8.1 to 11.6 respectively.

The best solutions of Numerical Optimization for ITCZ-HPMC5CP, ITCZ-HPMCK4M and ITCZ-HPMC10CP, ITCZ-RS30D, ITCZ-EPO and ITCZ-E100, ITCZ-PVPHPMC50CP, ITCZ-PVPNaCMC and ITCZ-PVPHPMC5CMK4M with highest desirability value of 0.689, 0.868, 0.657, 0.769, 0.750, 0.741, 0.578, 0.754, 0.544 respectively. The statistics of most desired numerical optimization revealed that the 95% Confidence interval
low (95% CI low) and 95% Confidence interval high (95% CI high) is in the range where process average fall into 95% of the time of Microencapsulation Efficiency, Particle Size, \(t_{50}\), Mucoadhesion time and Degree of Swelling for respective preparations.

The 95% Confidence Interval low (95% CI low) and 95% Confidence Interval high (95% CI high) for Microencapsulation Efficiency, Particle Size and \(t_{50}\) for ITCZ-HPMC5CP was 75.54% to 81.36%, 119.63m to 184.64m and 7.55h to 10.41h respectively. For ITCZ-HPMCK4M the values are 73.63% to 88.51%, 76.28m to 260.03m and 8.44h to 10.79h respectively. For ITCZ-HPMC10CP the values are 65.14% to 87.72%, 118.02m to 205.4m and 5.29h to 7.15h respectively. For ITCZ-RS30D the values are 55.06% to 73.94%, 78.44m to 249.61m and 9.29h to 10.89h respectively. For ITCZ-EPO the values are 67.9% to 82.22%, 104.17m to 212.66m and 9.69h to 10.58 respectively. For ITCZ-E100 the values are 45.04% to 69.16%, 90.29m to 155.17m and 8h to 10h respectively. For ITCZ-PVPHPMC50CP Degree of swelling, Mucoadhesion time and \(t_{50}\) was 27.79% to 43.88%, 3.87h to 5.88h respectively. For ITCZ-PVPNaCMC the values are 25.49% to 35.73%, 4.65h to 6.63h and 8.96h to 10.55h respectively. For ITCZ-PVPHPMCK4M the values are 6.39% to 11.59%, 7.6h to 8.41h and 9.29h to 11.32h respectively.

The 95% Predictable Interval low (95% PI low) and 95% Predictable Interval high (95% PI high) for Microencapsulation Efficiency, Particle Size and \(t_{50}\) for ITCZ-HPMC5CP was 73.51% to 83.40%, 87.58m to 216.68m and 11.81h respectively. For ITCZ-HPMCK4M the values are 68.39% to 93.75%, 11.55m to 324.75m and 7.61h to 11.62h respectively. For ITCZ-HPMC10CP the values are 57.26% to 95.6%, 74.92m to 248.5m and 4.64h to 7.8h respectively. For ITCZ-RS30D the values are 50.36% to 78.64%, 35.89m to 292.15m and 8.89h to 11.28h respectively. For ITCZ-EPO the values are 63% to 87.13%, 67.03m to 249.8m and 9.38h to 10.89 respectively. For ITCZ-E100 the values are 38.39% to 75.82%, 72.35m to 173.1m and 6.22h to 8.39h respectively. For ITCZ-PVPHPMC50CP Degree of swelling, Mucoadhesion time and \(t_{50}\) was 22.14% to 49.54%, 3.16h to 6.59h respectively. For ITCZ-PVPNaCMC the values are 21.72% to 39.5%, 3.93h to 7.35h and 8.37h to 11.13h respectively. For ITCZ-PVPHPMCK4M the values are 4.31% to 13.66%, 7.28h to 8.73h and 8.48h to 12.13h respectively.

The Numerical Optimization revealed that the solutions obtained are based on overall ANOVA, diagnostic case statistics and desirability of the model. The Numerical
Optimization point out maximization of desirability function. The final formulations were selected on the basis of goals set for all responses obtained, criteria of attaining maximum microencapsulation efficiency, lowest possible particle size, best degree of swelling, better Mucoadhesion capacity and maximum time to reach half quantity of drug for sustain drug release.

Results based on overall goal set for optimized parameters and best fit model along with best regression analysis in terms of Microencapsulation efficiency, Particle size, Mucoadhesion time, Degree of swelling and Drug Release yielded the final formulations which are used further to carry out bioequivalence studies along with marketed innovator formulation.

Bioequivalence studies are generally conducted by comparing the in vivo rate and extent of drug absorption of a test and a reference drug product in healthy subjects. In a standard in-vivo bioequivalence study design, participants receive a single dose of test and reference products on separate occasions with random assignment to the two possible sequences of product administration. Samples of an accessible biologic fluid such as blood or urine are analyzed for drug concentrations, and pharmacokinetic measures such as area under the curve (AUC) and peak concentration (C_{max}), are obtained from the resulting concentration-time profiles. The procedure as per USFDA involves the calculation of a confidence interval for the ratio between the average values of the test and reference product. In the U.S., a test product is considered to be bioequivalent to a reference product if the 90% confidence interval of the geometric mean ratio of AUC and C_{max} between the test and reference fall within 80-125%. Currently, the bioequivalence limits of 80-125% have been applied to almost all drug products by the FDA.

In the Present Investigation, bioavailability and bioequivalence studies were carried out to study intra-subject variability of the drug as variability is the key issue for highly variable drugs such as Itraconazole. Parallel study design was constructed and in-vivo behavior of drugs was studied for the reference (Sporanox Capsules 100 mg) and selected test formulations. From the in-vivo data obtained pharmacokinetic parameters such as C_{max}, t_{max} and AUC were calculated and the best selected formulations were finalized having minimum variability for the study.
The Itraconazole (ITCZ) levels in rabbit plasma were estimated after oral administration of the innovator ITCZ pellets, developed Mucoadhesive microspheres and buccoadhesive film based formulation to rabbits in ratio of 10mg/kg body weight. Time course of plasma levels in the present study shows percentage of drug absorbed in two way study illustrating the variability behavior of the drug. The samples were collected over a period of 24 hrs starting from 0.5 hr.

The Results illustrates that the proposed modified release formulations (Muco-adhesive behavior) shows less variability as compared to immediate release marketed innovator product (Sporanox® Capsules 100 mg). The kinetic parameters were estimated in terms of $t_{\text{max}}$ (time to reach maximum plasma concentration), $C_{\text{max}}$ (maximum plasma concentration) and AUC (area under the curve). The 90 lower and 90 higher values found for Muco-adhesive patches was 89 and 112.1 respectively. The 90 lower and 90 higher values for HPMC based Mucoadhesive microspheres was 86.9 and 121.5 respectively and for Sporanox® (Innovator reference formulation) was 73.7 and 136.2 respectively.

The Geometric mean for test and for reference for Muco-adhesive patches was found to be 63 and 63.1 respectively. For Mucoadhesive HPMC based formulation the data are 51.6 and 50.2 respectively. The Sporanox® capsules shows data 50.5 and 50.5 respectively. The percent CV for test and reference was found to be 8.3 and 6.3, 56.5 and 14.3 and 25.4 and 19.9 respectively for the above said formulations. Area under curve was also calculated and 90 lower and 90 upper values for the tested three formulations was 79.9 and 106.4, 89.8 and 116.9 and for Sporanox® capsules was 81.6 and 141.4 respectively.

The Geometric Mean for test and reference for the three formulations tested was found to be 413.1 and 448.1, 198.9 and 291.7 and 294 and 273.8 respectively. The percent CV for developed and reference formulations were found to be 20.8 and 17.7, 23.17.4 and 29.6 and 26.7 respectively. 90 lower and 90 upper values for time to reach maximum plasma concentration ($t_{\text{max}}$) were found to be 77.7 and 68.3, 103.1 and 90.1 and 108.4 and 90.8 respectively. The Geometric mean for developed and reference formulations was found to be 3.78 and 4.86, 4.06 and 3.94 and 3.79 and 3.5 respectively. The percent CV for test and reference formulations was found to be 8.8 and 17.2, 12.6 and 11.6 and 16.3 and 24.4.
In Conclusion, the present study thus provokes the need for designing of dosage form in such a way so as to release the drug in a controlled manner reducing the intra-patient and inter-patient variability. An improvement in bioavailability and reduced inter-subject variability of Itraconazole may be attributable to the bioadhesive polymer. The variability of Itraconazole the drug used in research work can be reduced by modifying its release behavior.

The Results were independent of dosage form design provided the drug is getting released over an extended period of time. No significant adverse events were reported during the course of the study. The overall evaluation of laboratory results showed no significant changes or trends between screening and final examination. The vital signs of all the subjects recorded during the study were satisfactory. The formulations were safe and well tolerated at the dose given.